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Opinion

Ozone Therapy for Prevention and Treatment of COVID-19

Gregorio Martínez-Sánchez[1,2*]

[1]*Scientific Advisor, Freelance, Italy;* [2]*International Scientific Committee of Ozone Therapy (ISCO3), Madrid, Spain*

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Abstract

The pandemic of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), represents an unprecedented threat to health and the world economy. According to the scientific background and preliminary clinical trials, ozone therapy (OT) may help as complementary therapy in prophylaxis, treatment, and in the recovery of convalescents. During the COVID-19 pandemic, the number of registered clinical trials using OT on COVID-19 represented an increment of 36% compared to the total number of previously recorded clinical studies. At present, papers that report an intervention in COVID-19 patients total 25. Four trials have been done in prophylaxis, there are 3 manuscripts enrolled convalescents, and there is 1 meta-analysis. Manuscripts with outcomes, indexed in the MedLine database, represent 73%. The most widely used routes of administration for the intervention in COVID-19 patients are ozonated saline solution and major autohemotherapy. Preliminary results are encouraging, indicating that OT reduces inflammation indices, decreases the time of assisted respiration, decreases C-reactive protein, improves oxygen saturation, could decrease mortality, and makes polymerase chain reaction tests negative in shorter periods. When trained medical doctors follow the correct protocols and use certified devices, the improvements that have been reported allow the patients to recover more quickly. However, it is considered that larger clinical studies are needed.

Introduction

As of March 2022, the pandemic of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), has spread to more than 227 countries or territories. It has infected more than 476 million people and has caused more than 6.1 million deaths, with an approximately 1.3% fatality rate. This represents an unprecedented threat to health and the world economy. An effective specific treatment is not yet available for patients with COVID-19 infection. In terms of prevention of mortality, an analysis of 101 clinical trials involving 67,491 participants showed that corticosteroids are likely to reduce mortality while colchicine may reduce mortality. There is no convincing evidence yet that any of the other treatments have a benefit in this outcome when compared with standard care or each other.[1] Experiences in the past management of respiratory viral infections have provided insights into the treatment of COVID-19. Numerous potential therapies, including supportive therapy, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion, have been tentatively applied in clinical settings. Several of these therapies have provided benefits, but controlled clinical studies have not shown true efficacy for most of the more than 350 drugs under study. At the same time, work is being done on more than 150 types of vaccines, approximately 25% of which are currently in various phases of human trials.[1] In addition, many obstacles remain, including the logistical difficulties of delivering the vaccines to the worldwide population.[2] However, the development of an effective and safe vaccine is still some way off.[3] Ozone therapy (OT), as a complementary method,[4] has also had broad support as a therapeutic proposal. This perspective paper aims to review the main articles supporting the role of OT in prevention, complementary therapy, and support in convalescent patients of COVID-19. During the COVID-19 pandemic, the number of registered clinical trials using medical ozone on COVID-19 have represented a significant part of the total number of previously recorded clinical studies for ozone applications in medicine. Currently there are different clinical studies with outcomes from all over the

Keywords: Ozone; Ozone therapy; COVID-19; SARS CoV-2.

Abbreviations: COVID-19, Coronavirus Disease 2019; IL-6, Interleukin-6; ISCO3, International Scientific Committee of Ozone Therapy; MAH, Major autohemotherapy; MiAH, Minor autohemotherapy; NF-κB, Nuclear factor kappa B; Nrf2, Nuclear factor erythroid 2-related factor; O3SS, Ozonized saline solution; OT, Ozone therapy; PCR, Polymerase chain reaction test; RIO3, Rectal insufflation of ozone; SARS-CoV2, Severe Acute Respiratory Syndrome Coronavirus 2.

[*]**Correspondence to:** Gregorio Martínez-Sánchez, International Scientific Committee of Ozone Therapy (ISCO3), Madrid, Spain. ORCID: https://orcid.org/0000-0002-6628-7388. Tel: +39 333-335-8310, E-mail: gregorcuba@yahoo.it

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world, indicative of the value of this therapy as a complement to treatment of COVID-19 patients. The potential role of OT in this disease merits further research. Appropriated use of ozone is an effective adjuvant therapy that can modulate oxidative stress and inflammation and can modulate immune response, although additional randomized clinical trials are urgently required to establish its potential benefit in the treatment of COVID-19.

Ozone therapy and COVID-19

Currently in the Medline database (PubMed), there are 4,129 documents related to OT, of which 310 are clinical trials, 214 are randomized controlled trials, 61 are systematic reviews, and 34 are meta-analysis studies, which support the use of ozone in medicine. In addition, ClinicalTrials.gov (a database of clinical studies in the US National Institutes of Health) currently has 61 studies registered for OT (of which 3 have terminated, 25 have completed, 3 are active and not recruited, and 13 are recruited). Moreover, registered interventional clinical trials for the treatment and prevention of COVID-19 using OT included 22 clinical trials in the public clinical trials database, 7 of these with outcomes. Spain, Italy, China, and Iran have a record of 3 clinical trials. In addition, Cuba, Turkey, and Brazil have 2 clinical trials underway. Under clinical trials in groups using ozone, there are plans to recruit 999 COVID-19 patients. Most of the trials plan to use major autohemotherapy as the first administration method and rectal insufflation for the second. The number of studies related to the use of ozone in COVID-19 represents a high proportion (36%) in relation to the total number of studies registered on the use of ozone in medicine.

At present, 26 support reviews have been written about the mechanisms of OT as a complement in the prevention and treatment of COVID-19. Papers have been written by 100 authors of 11 nationalities. These authors are mainly from Italy (39%), Spain (15%), Iran (15%), and USA (13%). The main mechanisms supported are: Nuclear factor erythroid 2-related factor (Nrf2)-Nuclear factor kappa B (NF-κB) modulation, cytokines release modulation, improvement in hypoxia, improvement in blood flow, release of nitric oxide, modulation of the oxidative stress, cytoprotective effect, and ozone as a regulator of the intestinal microbiota.[5–12] The available clinical information resulting from clinical trials (Table 1) mainly focus on clinical, radiological, and laboratory indices. However, some cases have found the modulation of cytokine interleukin-6 (IL-6) by ozone.[13]

Presently, 33 scientific papers have been published with outcomes concerning the application of ozone in COVID-19 patients. Papers that report an intervention in the COVID-19 patients total 25 (508 patients), and 4 trials have been done in prophylaxis[14] involving 599 subjects. There are 3 manuscripts enrolling 189 COVID-19 convalescents[15] and 1 meta-analysis.[16] Manuscripts with outcomes, indexed in the MedLine database are 73%. The most widely used routes of administration for the intervention in COVID-19 patients are: ozonated saline solution and major autohemotherapy (Fig. 1). Scientists involved in clinical trials, using OT in COVID-19 number 163, and are mainly from Italy (54), India (35) and Spain (26). The countries that have created the most international research networks are Italy and Spain.

OT, despite being wrongly called “pseudoscience”, can actually be considered a “super science”. The analysis of the number of scientific publications on “Ozone Therapy”, in the PubMed central database of the National Library of Medicine of the United States, shows a growing trend (Fig. 2) in the number of papers that report study about the molecular, preclinical, and clinical support of this therapy. It is noteworthy that, in the last 2 years, the trend is to the appearance of 4 daily articles on this subject. This places OT in a good position, as far as scientific support is concerned.

In addition, the International Scientific Committee of Ozone Therapy (ISCO3) library (www.isco3.org), in March, 2022 included 3,740 scientific articles on OT. Of these, 20%, a total of 763, correspond with preclinical research articles. The three fields where preclinical research is most concentrated are: sepsis, the antioxidant effects of ozone, and its actions on the musculoskeletal system, mainly on its analgesic effects. Moreover, ISCO3 library includes 2,538 clinical studies, which represent 68% of the total records. The first 3 areas in which ozone is used are: musculoskeletal diseases with 31%, which is mainly for the treatment of low back pain and knee pain. Next, with 16%, concerns the applications of OT in dentistry. The third place is for dermatological diseases, within which 68% represent the cure of ulcers, wounds, and diabetic foot. The database also indexes 21 meta-analysis studies and 234 literature reviews, focused on the clinical applications of ozone.

A preliminary report of an ongoing study in Italy of 46 COVID-19 patients (11 intubated and 35 non-intubated) showed that in 39 (84%) of the patients, an improvement was seen. In addition, a series of clinical studies (Table 1) has shown clinical, radiological, and laboratory improvement in patients treated with ozone, without side effects.

Despite this scientific background of studies on the potentials of medical ozone as a complementary therapy, medical ozone is still branded as a “biocide” (substance that is intended to destroy, counteract, neutralize, impede the action of, or exercise a control of another type on any organism considered harmful to humans) or “pseudoscience” (false treatment that is presented as scientific). This denotes a total ignorance of the concept of medical ozone defined in the Madrid Declaration on Ozone Therapy[4] which defines basic aspects, such as the type of devises, qualification and preparation of the personnel that conduct therapies and safe standard medical protocols.

In this way, medical ozone is marginalized as an “orphan drug” (drug not widely developed by the pharmaceutical industry for financial reasons, since they are intended for a small group of patients, but which, nevertheless, respond to public health needs). In fact, most OT research is carried out by the private sector, as public funds are scarce to support these studies. In terms of costs, it is worth clarifying that most OT is applied in private clinics and this affects the cost of treatment to the patient. However, if this procedure were introduced in the public sector, the savings in resources, medicines, and length of hospital stays would have a great impact in terms of health economics, as some studies have suggested.[39,40]

Future directions

It can be said that at present, there are scientific premises to carry out larger clinical studies which allow the introduction of OT in the complementary treatment of pathologies of high incidence in the population, such as infectious diseases, diabetes and its complications, pain control, diseases where hypoxia are involved, and others. In particular in the case of COVID-19, the preliminary results are encouraging, in the sense that when trained medical doctors follow the correct protocols and use certified devices, the improvements that have been reported allow the patients to recover more quickly.

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Table 1. Main outcomes of the current studies of ozone in COVID-19 patient, in prevention and in the treatment of sequalae

Number of patient/controls. Remarks	Protocol	Outcomes	Reference
Ozone in prophylaxis of COVID-19			
9/0 Patients with sub-clinical symptoms of COVID-19	RiO3 once a day for 5 days and 1 week later.	Reduction of Telomere unit (BDORT Unit) from 14.219 at baseline to 0 at day 5. Pain intensity reduction. No changes in IL6 or PCR.	Falzoni *et al.* (2021)[17]
320 subject/Community prevalence	8 MiAH, Vit. D, B12 in 2 months.	Reduction in the incidence of COVID-19 2.19% vs 18.98%.	Shah *et al*. (2020)[18]
64/171 Health Care Workers	4 O3SS one a day, follow 1 month.	Significant ($p = 0.04$) decrease in rate of incidence of COVID-19: 4.6% vs 14.03%	Sharma *et al.* (2020)[14]
35 subject/Community prevalence	8 MiAH one every 15 days, plus 1 session a month for 3 months.	Decrease in rate of incidence of COVID-19 to 2.8%	Ordóñez and de las Mercedes (2021)[19]
Ozone in treatment of COVID-19			
9/9	2 MAH a day for 4 days.	Shorter mean time to clinical improvement.	Hernández *et al*. (2021)[20]
30/30	2 RiO3 a day + 1 MiAH daily for 10 days.	Improve RT-PCR negative reaction ($p = 0.01$), improve in clinical symptoms ($p < 0.05$) and reduction in requirement for Intensive care ($p < 0.05$).	Shah *et al*. (2021)[21]
48/44	MAH daily for 3 consecutive days.	Did not show any effect on mortality, or mechanical intubation, but show a clinical improvement at day 7 from randomization, in a composite clinical endpoint.	Sozio *et al.* (2021)[22]
50/0 vs historical control	MAH daily, 3–5 session.	Improvement of major respiratory indexes and blood gas parameters. Significant reduction of inflammatory and thromboembolic markers (CRP, IL-6, D-dimer).	Franzini *et al.* (2020)[13]
30/30	MAH daily for 3 consecutive days.	Significant clinical improvement in ozone group.	Tascini *et al*. (2020)[23]
9/9	2 MAH a day for 4 days.	Significantly shorter time to clinical improvement in ozone group.	Hernández *et al*. (2020)[24]
2/0 vs historical control	MAH once daily for 7 consecutive days.	Ozone therapy may promote recovery of clinical condition and improvement of chest CT images, shorten the duration of viral shedding and length of hospital stay.	Zheng *et al*. (2020)[25]
14/14	MAH twice daily for 7 consecutive days.	Ozone therapy had an impact on the need for the ventilatory support, although didn't reach statistical significance.	Araimo *et al*. (2020)[26]
25/0 vs historical control	O3SS once daily for 10 consecutive days.	Improvements in symptoms and laboratory results including: D-dimer, fibrinogen, lactate dehydrogenase, and C-reactive protein.	Schwartz *et al.* (2021)[27]
5/0	MAH treatments in 5 days.	Significant clinic improvement.	Junping *et al.* (2020)[28]
82 moderate: severe/0, 16 critical/0	O3SS for 5–10 days with 1–2 doses per day.	Shorter hospitalization and faster recovery.	Razzaq *et al.* (2020)[29]
4/0	RIO3, 5 sessions (1 session/day)	Improved oxygen saturation, biomarkers of inflammation decreased and improves Taylor's radiological grade.	Fernández-Cuadros *et al*. (2020)[30]
9/9	MAH, twice daily starting on the day of admission for a median of 4 days.	Significantly ($p = 0.01$) shorter time to clinical improvement.	Hernández *et al*. (2020)[31]

(continued)

Table 1. *(continued)*

Number of patient/controls. Remarks	Protocol	Outcomes	Reference
1/0	RIO3, 5 sessions (1 session/day).	Improved oxygen saturation, biomarkers of inflammation decreased and improves Taylor's radiological grade.	Peña-Lora *et al.* (2020)[32]
19/18	O3SS ones daily for 10 days.	Improvement in laboratory, radiological and clinical tests.	Hammad *et al.* (2020)[33]
14/ case control	RIO3, 8 sessions (1 session/day).	Improved oxygen saturation, biomarkers of inflammation decreased and improves Taylor's radiological grade.	Fernández-Cuadros *et al.* (2021)[34]
2/0	RIO3, 1/2 sessions a day until discharged.	Clinical improvement.	Hendawy *et al.* (2021)[35]
55/18	MAH daily for 7 days.	OT could reduce mortality.	Çolak *et al.* (2021)[36]
10/0	O3SS once daily for 8 days.	Resolved clinical symptoms, improved oxygenation, clearance of infiltrates on chest X-ray and improvement in biomarkers in a short period.	Sharma *et al.* (2021)[37]
1/0	RIO3 daily for 10 days continuing with O3SS once daily for 8 days.	Clinical improvement.	Cachay-Morales, J. & Cachay-Agurto J. (2021)[38]

Note: No adverse effects were noticed in any of the studies cited in the table. Legend: MAH, Major autohemotherapy; MiAH, Minor autohemotherapy OT, Ozone therapy; RIO3, Rectal insufflation of ozone; O3SS, ozonized saline solution.

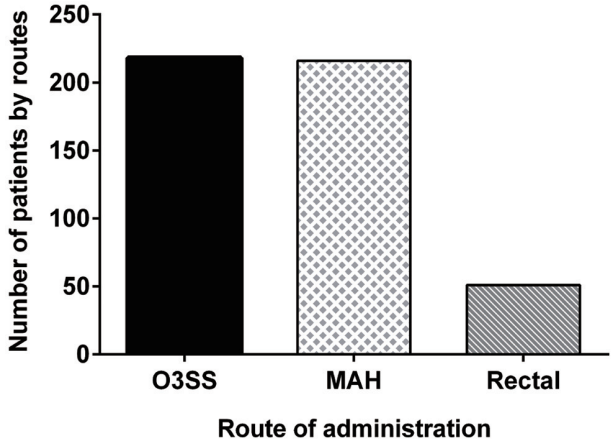

Fig. 1. Number of COVID-19 patients treated with ozone by route of administration in clinical trials with outcomes. O3SS, ozonized saline solution; MAH, major autohemotherapy.

Conclusions

In COVID-19, the main results of the studies indicate that ozone reduces inflammation indices, decreases the time of assisted respiration, decreases C-reactive protein, improves oxygen saturation, could decrease mortality, and make PCR results negative in shorter periods. Despite preliminary data from current clinical trials, as well as expert opinions, it is considered that there is still not enough evidence to confirm OT as a viable treatment option for COVID-19. Therefore, larger clinical studies are needed.

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Conflict of interest

Gregorio Martínez-Sánchez is Chairman of International Scientific Committee of Ozone Therapy.

Author contributions

GMS was the sole author.

Data sharing statement

Data supporting reported results can be found in the ISCO3 virtual library www.zotero.org/groups/46074/isco3_ozone/library, section Ozone therapy/Clinical/Infection diseases/Covid-19.

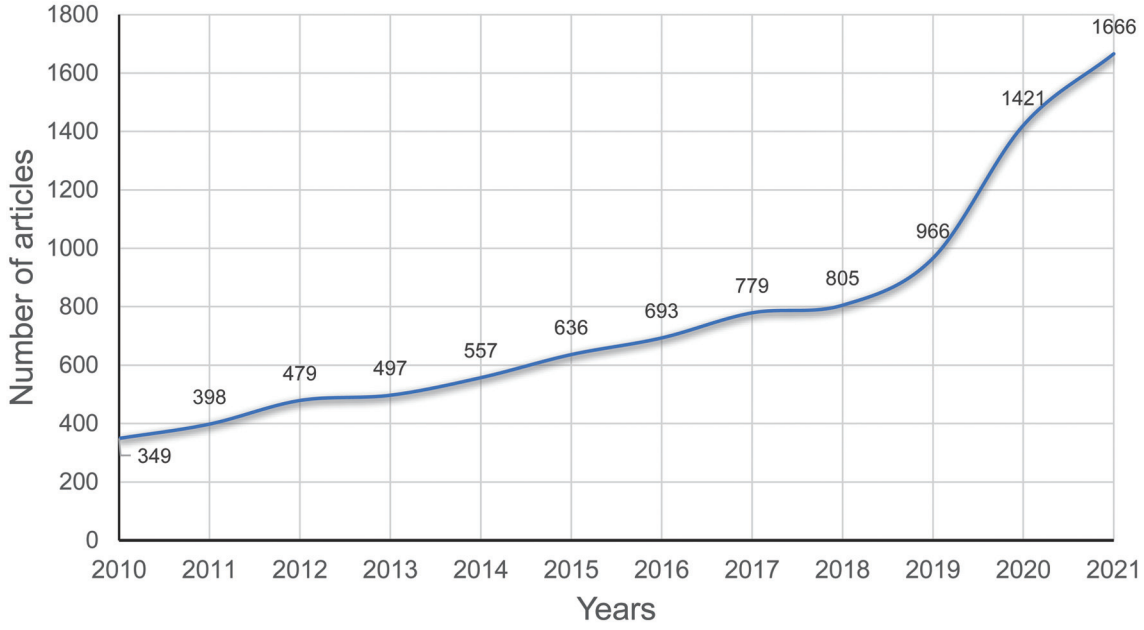

Fig. 2. Number of articles by years with the keywords "ozone therapy" in PubMed Central. Sources: Pub Med Central (US National Library of Medicine, National Institutes of Health), 2021.

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